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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,515	08/07/2001	Rosanne M. Crooke	ISIS.019A	1714

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,515	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 22, April 27, June 30, 06'*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,9,10,12,15 and 41-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,12,41,45,46 and 54-56* is/are rejected.

7)☒ Claim(s) *7, 9, 10, 15, 42-44, 47-53, 57, and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence search alignment*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :November 25, 2005, January 23, 2006, April 28, 2006, June 30, 2006, and August 30, 2006 .

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed February 22, 2006, April 27, 2006, and June 30, 2006.

Claim 13 has been canceled. Claims 1, 15, and 41 have been amended. New claims 51-58 are acknowledged.

Claims 1, 5, 7, 9, 10, 12, 15, and 41-58 are pending in the instant application.

Claims 1, 5, 7, 9, 10, 12, 15, and 41-58 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statements filed November 25, 2005, January 23, 2006, April 28, 2006, June 30, 2006, and August 30, 2006 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements and signed copies are enclosed herewith.

The Examiner also acknowledges Applicant's information disclosure statement filed December 21, 2005 in which Applicants corrected the inadvertent omitted material regarding the number of months in the statement regarding the length of time for which an individual designated in 37 C.F.R. § 1.56(c) had knowledge of the listed reference.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed September 22, 2005, claims 1, 5, 7, 9, 10, 12, 13 and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. [WO 99/35241] in view of McLean et al. (Nature, 1987 Vol. 330:132-137), and Baracchini et al. [U.S. Patent No. 5,801,154]. **This rejection is moot** against claim 13 in view of Applicant's Amendment to cancel this claim. **This rejection is withdrawn** against claims 1, 5, 7, 9, 10, 12, and 15 in view of Applicant's Amendment. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite nucleotides 174 to 203 or SEQ ID NO:7. It is noted that the combination of Rouy et al., McLean et al., and Baracchini et al. would not render the instant invention obvious, at the time the instant invention was made.

Applicant's Amendment necessitated the new grounds of rejection presented below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 12, 41, 45, 46, 54, 55, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rouy et al. [U.S. Patent No. 6,512,161] ('161) in view of Skerra et al. (Nucleic Acids Research, 1992 Vol. 20:3551-3554).

Claim 1 is drawn to a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3, has 100% complementarity to SEQ ID NO:3, and comprises at least one modification selected from the group consisting of a modified internucleoside linkage, a modified sugar moiety, and a modified nucleobase. Claims 5, 12, and 56 are dependent on claim 1 and include all the limitations of claim 1 with the further limitations, wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein said oligonucleotide is targeted to nucleotides 174 to 193 of SEQ ID NO:3; and the non-cleaving antisense oligonucleotide of claim 1 and a pharmaceutically acceptable carrier or diluent. Claim 41 is drawn to an antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide comprises at least an 8-nucleobase portion of the nucleobase sequence of SEQ ID NO:7 and has 100% complementarity to a nucleic acid molecule encoding human apolipoprotein(a) (SEQ ID NO:3). Claims 45, 46, and 54 are dependent on claim 41 and include all the limitations of claim 41 with the further limitations wherein the oligonucleotide comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a

phosphorothioate linkage, and the an antisense oligonucleotide of claim 41 and a pharmaceutically acceptable carrier or diluent. Claim 55 is dependent on claim 41 and includes all the limitations of claim 41, with the further limitation being the antisense oligonucleotide of claim 41 having at least 12 linked nucleobases of SEQ ID NO:7. It is noted that SEQ ID NO:7 of the instant invention is complementary to nucleotides 174 to 192 of SEQ ID NO:3 of the instant invention and thus falls within and reads on a sequence targeting nucleotides 174 to 203 of SEQ ID NO:3 as claimed.

'161 teaches an apolipoprotein(a) reverse transcription primer with the following sequence: 5'-GATGACCAAGCTTGGCAGGTTCTTCC-3 (see SEQ ID NO:3). It is noted that this primer is 100% complementary to nucleotides 187-203 of SEQ ID NO:3 of the instant invention (see attached sequence alignment). It is further noted that this primer comprises at least an 8-nucleobase portion of SEQ ID NO:7 (see attached sequence alignment at nucleotides 174-182). It is further noted that the primer taught by '161 is almost 100% complementary to all of nucleotides 181 to 203 of SEQ ID NO:3, having only one mismatch (see attached sequence alignment). Since this primer is almost fully complementary, containing only one mismatch, it meets the structural limitations of the claimed invention and would be expected to "target nucleotides 174 to 203 of SEQ ID NO:3" since the instant specification at page 9, first full paragraph teaches, "[A]ntisense and other compounds of the invention... hybridize to the target" and the instant specification at pages 8 and 9, lines 35 and 1-2, respectively teaches, "[I]t is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable."

The Examiner would like to point out that the apolipoprotein(a) reverse transcription primer disclosed by '161 was used in a PCR reaction containing several buffers, all of which constitute pharmaceutically acceptable carriers. Accordingly, the apolipoprotein(a) reverse transcription primer disclosed by '161 has 100% complementarity to SEQ ID NO:3, comprises at least an 8-nucleobase portion of SEQ ID NO:7, and would target nucleotides 174 to 203 of SEQ ID NO:3 as claimed.

The burden of establishing whether the prior art primer functions as a non-cleaving antisense oligonucleotide, under generally any assay condition, falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence

that the apolipoprotein(a) reverse transcription primer disclosed by '161 would or would not have the additional functional limitation of functioning as a non-cleaving antisense oligonucleotide as instantly claimed.

'161 does not teach wherein the oligonucleotide comprises at least one modification selected from the group consisting of a modified internucleoside linkage, a modified sugar moiety, and a modified nucleobase.

Skerra, A. teaches phosphorothioate-modified primers improve the amplification of DNA sequences by DNA polymerase with proofreading activity (see Abstract). Skerra, A. teaches the introduction of single phosphorothioate bond at the 3' termini of the PCR primer protects the oligodeoxynucleotide from exonucleolytic attack leading to specific and efficient amplification of DNA.

It would have been *prima facie* obvious to one of ordinary skill in the art to make a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3, has 100% complementarity to SEQ ID NO:3, and comprises at least one modification using the teachings of '161 and following the method and motivation of Skerra, A.

One of ordinary skill in the art would have been motivated to make a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3, has 100% complementarity to SEQ ID NO:3, and comprises at least one modification since '161 explicitly taught the nucleic acid in the form of a primer and Skerra taught the introduction of single phosphorothioate bond on the PCR primer protects the

oligodeoxynucleotide from exonucleolytic attack leading to specific and efficient amplification of DNA.

One of ordinary skill in the art would have expected success at making a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3, has 100% complementarity to SEQ ID NO:3, and comprises at least one modification because the oligonucleotide of '161 is a primer used for PCR and Skerra taught the successful design and use of phosphorothioate-modified primers in the amplification of DNA sequences during PCR.

Therefore the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

Conclusion

No claims are allowable.

Claims 7, 9, and 10 are objected to as being dependent upon a rejected base claims, but would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Claims 7, 9, and 10 are considered to be free of the prior art since the prior art does not teach or fairly suggest a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3, has 100% complementarity to SEQ ID NO:3, and comprises at least one modification, wherein the modification is a modified sugar moiety being a 2'-O-methoxyethyl sugar moiety, a 5-

methylcytosine, or a chimeric oligonucleotide. Claim 15 is objected to as being dependent upon a rejected base claims, but would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Claim 15 is considered to be free of the prior art since the prior art does not teach or fairly suggest a method of inhibiting the expression of human apolipoprotein(a) in cells or tissues *in vitro* comprising contacting said cells or tissues with a non-cleaving antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide is targeted to nucleotides 174 to 203 of SEQ ID NO:3; has 100% complementarity to SEQ ID NO:3. Claims 42-44, 47-53, 57 and 58 are objected to as being dependent upon a rejected base claims, but would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Claims 42-44, 47-53, 57 and 58 are considered to be free of the prior art since the prior art does not teach or fairly suggest an antisense oligonucleotide 12 to 30 nucleobases in length, wherein said oligonucleotide comprises at least an 8-nucleobase portion of the nucleobase sequence of SEQ ID NO:7 and has 100% complementarity to a nucleic acid molecule encoding human apolipoprotein(a) (SEQ ID NO:3), wherein said oligonucleotide is 20 nucleobases in length; wherein said oligonucleotide comprises or consist of SEQ ID NO:7, wherein said oligonucleotide comprise modified sugar moiety being a 2'-O-methoxyethyl sugar moiety, a 5-methylcytosine, or a chimeric oligonucleotide, and wherein said chimeric oligonucleotide comprises a gap segment.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
September 6, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635

Sequench search alignment...

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RESULT 2
AR278865/c
LOCUS       AR278865                 26 bp    DNA     linear   PAT 10-APR-2003
DEFINITION  Sequence 3 from patent US 6512161.
ACCESSION   AR278865
VERSION     AR278865.1  GI:29713382
KEYWORDS    .
SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 26)
  AUTHORS   Rouy,D., Duverger,N., Emmanuel,F., Denefle,P., Houdebine,L.-M.,
            Viglietta,C., Rubin,E.M. and Hughes,S.D.
  TITLE     Transgenic rabbit that expresses a functional human lipoprotein (a)
  JOURNAL   Patent: US 6512161-A 3 28-JAN-2003;
            Aventis Pharmaceuticals, Inc.; Bridgewater, NJ
FEATURES             Location/Qualifiers
     source          1. .26
                     /organism="unknown"
                     /mol_type="genomic DNA"

  Query Match             59.5%;  Score 24.4;  DB 1;  Length 26;
  Best Local Similarity   96.2%;  Pred. No. 0.33;
  Matches   25;  Conservative    0;  Mismatches    1;  Indels    0;  Gaps    0;

Qy        181 GGAAGGACCTGCCAAGCTTGGTCATC 206
              ||||| ||||||||||||||||||||||
Db         26 GGAAGAACCTGCCAAGCTTGGTCATC 1
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